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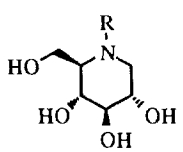
Synthesis of N-Alkoxytrihydroxypiperidine Analogs of Allopyranose

Lihong Sun, Pan Li, Donald W. Landry,†* and Kang Zhao*

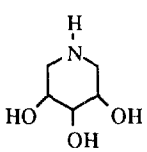
Department of Chemistry, New York University, New York, NY 10003; †Department of Medicine, Columbia University, College of Physicians & Surgeons, New York, NY 10032

Summary: *Tandem reductive cyclization of O-alkyl oximes provides an efficient method for the preparation of N-alkoxytrihydroxypiperidine analogs of allopyranose as potential glycosidase inhibitors.*

Glycosyltransferases and glycosidases modify the glycoconjugates of proteins and lipids and these enzymes are essential for normal cell growth, metabolism, and development.[1,2] Unregulated activity of these enzymes has consistently been observed in cells which are transformed by chemical mutagens, oncogenic viruses, or neoplastic cell DNA.[3] Specific inhibitors have made possible the elucidation of the function of these enzymes in normal and pathological states.[4] Continued efforts in the development of powerful inhibitors may provide leads to potential applications in the treatment of viral diseases, such as influenza,[5] HIV,[4a-b] and certain leukaemia.[6] Specifically, 1-deoxynojirimycin **1** (DNJ) and N-*n*-butyl deoxynojirimycin **2** (BuDNJ) are potent glycosidase inhibitors and anti-HIV agents.[5a-b] Recently, Ganem *et al.* have also found that several trihydroxypiperidine derivatives **3**, lacking C6-hydroxymethyl substituents, are comparable to DNJ as glycosidase inhibitors.[7]



1, R=H; **2**, R=*n*-Butyl



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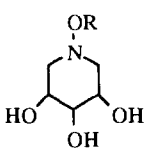
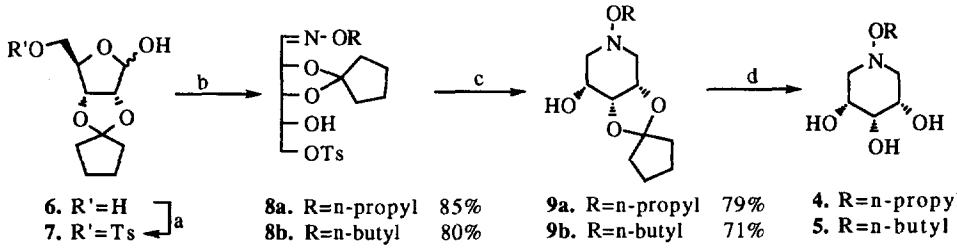


4, R=*n*-Propyl; **5**, R=*n*-Butyl

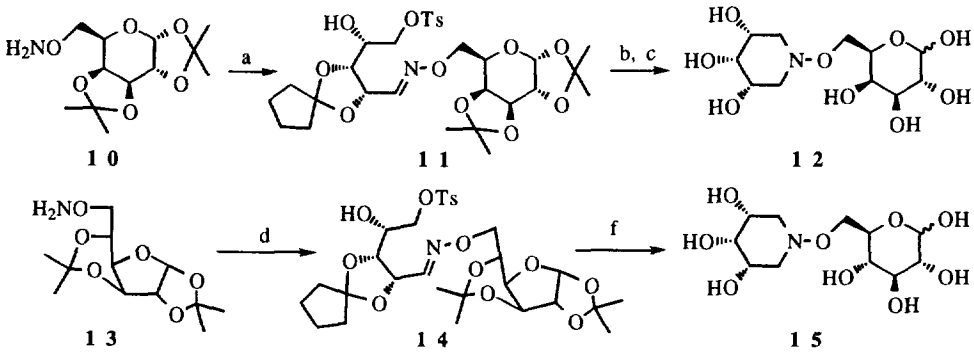
The catalytic site of these enzymes contains both carboxylic acid and carboxylate moieties and the initial interaction at this site can occur with the free amine or ammonium salt of the piperidine inhibitor.[8] The attachment of an electron-withdrawing alkoxy group to nitrogen could, by moving the pKa of the inhibitors towards the physiological pH range, provide a novel class of more effective inhibitors. Herein, we report a procedure for the efficient synthesis of N-alkoxytrihydroxypiperidines **4**, **5**, **12** and **15**.[9]



6. R'=H
7. R'=Ts
a
8a. R=n-propyl 85%
8b. R=n-butyl 80%
9a. R=n-propyl 79%
9b. R=n-butyl 71%
4. R=n-propyl
5. R=n-butyl

Scheme 1. (a) TsCl (1.1 eq.), Pyridine, 0 °C-r.t. 95%; (b) $RONH_2HCl$ (1.3 eq.), NaOH (1.2 eq.), MeOH, pH=6-7, r.t.; (c) i. $NaCNBH_3$ (3 eq.), HOAc; ii. $(CH_2NH_2)_2$; (d) Dowex-50WX8 (H^+), H_2O.

The synthesis began with 2,3-O-cyclopentylidene-ribofuranose **6**, readily prepared from D-ribose.[10] Selective tosylation of the primary hydroxyl group of **6** and then treatment of the resulting tosylate **7** with O-propyl hydroxylamine[11] gave oxime **8a** in 85% yield. Among the various methods available,[12] a relatively mild method for the reduction of O-acetyl and O-benzyl oximes consists of $NaCNBH_3$ in acetic acid.[13] Treatment of oxime **8a** with excess of $NaCNBH_3$ in acetic acid at room temperature for 1 h, followed by neutralization with ethylenediamine for 30 minutes directly afforded **9a** in 79% yield.[14] Deprotection was conducted with acidic Dowex in water to afford N-propoxytrihydroxypiperidine **4** in quantitative yield. The tosylate **7** was similarly converted to **5** (R = *n*-butyl) in 57% overall yield.



Scheme 2. (a) **7** (1 eq.), benzene, reflux. (b) $NaCNBH_3$ (3 eq.), HOAc; then $(CH_2NH_2)_2$. (c) Dowex-50WX8 (H^+), H_2O, 70% overall yield from **7**. (d) **7** (1 eq.), PPTS (cat.), MeOH, r.t., 95%. (f) = b, c, 75%

Glycosidases generally recognize the two sugar fragments between reaction centers, and therefore specific inhibitors can be designed containing structural features of both portions.[2] Our interest was in the preparation of pseudodisaccharide **12** containing an iminosugar and a saccharide unit, which are connected to each other

by a N-O bond (Scheme 2). Treatment of furanose **7** with O-aminosugar derivative **10**[15] produced the oxime **11**. The reductive cyclization of **11**, employing the above described procedure, gave an intermediate which was hydrolyzed to pseudodisaccharide **12** in 70% overall yield. The corresponding glucose analog **15** was prepared in a similar manner from the readily available material **13**.[16]

The reported procedures are concise and efficient in connecting an aglycon moiety to sugar analogs via N-O linkage. The derived N-alkoxytrihydroxypiperidines **4**, **5**, **12** and **15** represent a new class of iminosugar analogs. Furthermore, these N-alkoxypiperidines are less basic than the corresponding piperidine analogs and thus may provide a good model for the mechanistic studies for the pH-dependent glycosidase inhibition.[8,17] Such studies are currently in progress in our laboratory and will be reported elsewhere.

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14. Compound **9a:** ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* 7.3 Hz, -$OCH_2CH_2C\underline{H}_3$), 1.50 (2H, m, -$OCH_2C\underline{H}_2CH_3$), 3.55 (2H, t, *J* 6.7 Hz, -$OC\underline{H}_2CH_2CH_3$), 1.56-1.96 (8H, m, cyclopentyl), 2.50-2.80 (3H, m, 5-OH, H_{1a}, H_{5a}), 3.12 (1H, dd, $J_{4a,5e}$ 3.7, $J_{5e,5a}$ 10 Hz, H_{5e}), 3.17 (1H, dd, $J_{1e,2a}$ 3.7, $J_{1e,1a}$ 11 Hz, H_{1e}), 4.00 (1H, m, H_{4a}), 4.11 (1H, t, $J_{2a,3e} = J_{3e,4a} = 4.0$ Hz, H_{3e}), 4.24 (1H, m, H_{2a}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.11, 22.45, 75.15 (*n*-propyl), 23.97, 24.29, 38.11, 38.39, 119.95 (cyclopentyl), 56.19 (C_5), 57.14 (C_1), 65.93 (C_4), 72.59 (C_2), 74.14 (C_3).
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16. Compound **13** was prepared from 1,2-isopropylidene-glucofuranose by the following steps: a) 1.2 eq. of TsCl, py, r.t. b) 2-Methoxypropene, TsOH, DMF, 0 °C, 57%. c) LiBr, Et_3N, N-Hydroxyphthalimide, DMF, 100 °C, 50%. (e) NH_2NH_2, MeOH, r.t., 97%.
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